CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020357, S017

Trade Name: GLUCOPHAGE TABLETS

Generic Name: METFORMIN HYDROCHLORIDE

Sponsor: BRISTOL-MYERS SQUIBB

Approval Date: 09/22/99

INDICATION(s): IS INDICATED AS AN ADJUNCT TO DIET TO LOWER BLOOD GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES WHOSE HYPERGLYCEMIA CANNOT BE SATISFACTORILY MANAGED ON DIET ALONE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020357, S017

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020357, S017

APPROVAL LETTER

NDA 20-357/S-017

SEP 22 1999

Bristol-Myers Squibb
Attention: Mr. Warren Randolph
Director, U.S. Regulatory Liaison
P.O. Box 4000
Princeton, NJ 08543-4000

APPROVED

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated March 3, 1999, received March 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage® (metformin hydrochloride) Tablets, 500 mg, 850 mg, and 1000 mg.

This supplemental new drug application provides for the deletion of the entire subsection titled "Special Warning on Increased Risk of Cardiovascular Mortality", of the **WARNINGS** section of the package insert. Also, question 17 is deleted from the patient package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted March 3, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-357/S-017." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

/S/ 4/22/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S017

MEDICAL REVIEW(S)

NDA 20-357 /S-017 MOR
Glucophage – Metformin HCl
Submission of March 3, 1999
Bristol-Myers Squibb

BMS is requesting that they be allowed to remove from the glucophage label the Special Warning of Increased Risk of Cardiovascular Mortality, which came from the findings of the University Group Diabetes Program (I shall refer to this subsequently as the UGDP Warning).

The justification for the removal of the UGDP warning is new data from the United Kingdom Prospective Diabetes Study (UKPDS) which contradict the findings of UGDP. This submission contains reprints of two Lancet articles from UKPDS and a discussion paper about the differences between the findings of UKPDS and UGDP.

UGDP was a study in previously untreated patients with mild diabetes. Patients received one of five treatments, tolbutamide, phenformin, placebo, fixed dose insulin or variable dose insulin. Although all the drug treatments were more effective than placebo in lowering blood glucose levels, patients on tolbutamide or phenformin showed an apparent increased risk of cardiovascular mortality. For this reason the study was terminated prematurely. There followed a lengthy debate about the validity of the conclusions of UGDP. A detailed critique of UGDP is beyond the scope of this review. Suffice it to say that, most diabetologists appear to have concluded long ago that the results of the UGDP study were not correct. This statement by Daniel Foster appeared in the 11th edition of Harrison's Textbook of Medicine in 1987:

> "Fear the sulfonylureas might increase deaths from heart attacks, prompted by reports of the UGDP, has largely dissipated because of questions about the design of that study and failure of other studies to confirm risks."

Even without UKPDS, the view expressed by Dr Foster in 1987 seems to have been vindicated. In a long-term follow-up of patients with impaired glucose tolerance, Knowler et al concluded that tolbutamide probably decreased total mortality and mortality from ischemic heart disease (Diabetologica 1997; 40: 680-686).

Based on the findings with tolbutamide, FDA has mandated a UGDP warning of possible increased cardiovascular mortality in the labels of ALL sulfonylureas, not just tolbutamide. Phenformin also had this warning but was removed from the market in 1977 because of lactic acidosis. However, when metformin was approved in 1995, its label also contained a UGDP warning. In view of the results of UKPDS it is now time for FDA to reconsider the wisdom of retaining this warning.

UKPDS was a long-term study comparing conventional treatment (diet only) to insulin and sulfonylureas. A secondary analysis compared 342 overweight patients allocated to metformin with 951 patients allocated to chlorpropamide(n= 265), glyburide (n= 277) or insulin (n=409). All oral agents were titrated to maximal tolerated dose. Metformin was given as two 850 mg tablets in the morning and one in the evening. Median HbA1c during the 10 years of follow-up was reported to be 7.4% in metformin patients compared to 8.0% in conventionally treated patients. HbA1c was reported to be similar among all drug-treated patients. Major hypoglycemic events were the same in conventionally treated patients (0.7%) and metformin-treated (0.6%) but were higher in patients treated with SFU's (1.1`%) or insulin (2%). Weight gain was approximately the same in conventional and metformin patients (about 1.5 kg in 10 years). Weight gain was greater in SFU-treated (about 4 kg) and insulin-treated (about 6 kg) patients. Of particular interest are differences in endpoints related to diabetic complications. Metformin was significantly better than conventional treatment with respect to diabetes-related death, all-cause mortality and myocardial infarction, with positive trends for stroke, peripheral vascular disease and microvascualr complications. The relative risk for any diabetes-related endpoint was 0.68 (95% conf 0.53-0.87). Metformin was significantly better than other drugs with respect to all-cause mortality, stroke and the aggregate "any diabetes endpoint". Diabetes related death and myocardial infarction were also less with metformin than

with other intensive therapy but the p values were 0.11 for diabetes-related death and 0.12 for myocardial infarction. The authors of UKPDS interpreted the results as follows:

> " Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycemic attacks than are insulin and sulfonylureas, it may be the first-line pharmacological therapy of choice in these patients."

An apparent contradiction to the monotherapy results is that the addition of metformin to patients inadequately controlled on a sulfonylurea alone resulted in an increase in all-cause mortality and diabetes-related death. The authors largely dismiss this result as being inconsistent with their review of epidemiological data. They also point out that patients on combined therapy were older and had higher glucose levels

Publication of the UKPDS data was accompanied by an editorial from Dr Robert Nathan. Dr Nathan also contributed to a position paper published by the American Diabetes Association, which expressed skepticism about the decrease in mortality when metformin was used alone and the increase in mortality when metformin was used in combination with sulfonylureas. However, they do conclude that UKPDS has shown that neither sulfonylureas nor metformin appear to increase the risk of cardiovascular events, as might have been anticipated from the results of UGDP.

Since data from UKPDS were not submitted to FDA for review, it would not be appropriate to take any major action based exclusively on the published results. The presentation of data in the publications is very confusing and certain critical pieces of information are omitted. In particular we do not know what statistical techniques were used to account for dropouts and for patients who were switched from conventional to drug treatment. That conclusions about metformin are based on secondary analyses of obese patients and patients who failed on SFU treatment alone is particularly problematic.

Conclusion:

The authors of UKPDS suggest that metformin may be the treatment of choice for overweight patients with type 2 diabetes. The results are consistent with previous observations that metformin exerts favorable effects on body weight, serum lipids, and plasminogen activator inhibitor I, all of which would be expected to decrease morbidity from cardiovascular events. Since DMEDP has not reviewed the UKPDS data directly, we could not allow any superiority claims to be made for metformin. However, the possibility that the UKPDS data are completely bogus seems very remote. At a very minimum, the UKPDS has demonstrated that previous concern from UGDP, that metformin may increase cardiovascular death, was incorrect. The UGDP warning puts metformin at an unfair disadvantage relative to the thiazolidinediones, and should be removed from the metformin label.

Recommendation:

The label revision put forward in the supplement should be approved.

/S/

Robert I Misbin MD
HFD 510
September 3, 1999

Concur

9/8/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S017

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Exclusivity Checklist

NDA: 20-357 / S-017				
Trade Name: GLUCOPHAGE				
Generic Name: METFORMIN HCl				
Applicant Name: BMS				
Division: 510				
Project Manager: WEBER				
Approval Date: SEPT. 1999				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)	SE-8			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes		No	✓
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation: Deletion of a special warning regarding increased risk of cardiovascular mortality was based on review of a published study (UKPDS).				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	✓	No	
If yes, NDA # 20-357				
Drug Name: GLUCOPHAGE				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓

SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				

new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1	
Investigation #2	
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or

support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

/S/

Signature of PM/CSO
Date: 9/14/99

/S/

/S/

9/15/99

/S/

Signature of Division Director
Date: 9/22/99

/S/

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20357	**Trade Name:**	GLUCOPHAGE (METFORMIN HCL) 500 / 850 MG
Supplement Number:	17	**Generic Name:**	METFORMIN HCL
Supplement Type:	SE8	**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	This supplement proposes deleting the 3 paragraphs under the WARNINGS section of the Special Warning on Increased Risk of Cardiovascular Mortality subsection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

/S/ 9/15/99

/S/ 9/15/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENA WEBER

/S/

Signature

9/14/99

Date

PRAVACHOL® (Pravastatin Sodium) Tablets

DEBARMENT CERTIFICATION UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this supplemental application.

NDA 20-357/S-017

Warren C. Randolph September 15, 1999

APR 27 1999

NDA 20-357/S-017

Bristol-Myers Squibb
Attention: Mr. Warren Randolph
Director, U.S. Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Please refer to your efficacy supplemental new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Glucophage® (metformin hydrochloride) Tablets. You were notified in our letter dated March 22, 1999, that your application for Glucophage® (metformin hydrochloride) Tablets was not accepted for filing due to non-payment of fees.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of March 26, 1999.

The review priority classification for this application is Standard (S).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 25, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 26, 2000, and the secondary user fee goal date will be March 26, 2000.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Ms. Jena Weber, Regulatory Health Project Manager, at 301-827-6422.

Sincerely,

/S/ 4/27/99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-357/S-017

MAR 22 1999

Bristol-Myers Squibb
Attention: Mr. Warren Randolph
Director, U.S. Regulatory Liaison
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

We acknowledge receipt of your supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Glucophage® (metformin hydrochloride) Tablets

NDA Number: 20-357

Supplement Number: S-017

Date of Supplement: March 3, 1999

Date of Receipt: March 4, 1999

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this supplemental application is not accepted for filing. We will not begin a review of this supplemental application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: **This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number is on the enclosed check.**

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

/S/ 3.19.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA NO. 20357 REF NO. 017

NDA SUPPL FOR SE 4

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

MAR 0 4 1999

NDA 20-357
Glucophage ® (metformin hydrochloride) Tablets

March 3, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage ® (metformin hydrochloride) tablets, NDA 20-357. Additional reference is made to the package insert for this product and specifically to the SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY.

The Special Warning in the Glucophage® labeling derived from reported findings from the University Group Diabetes Program (UGDP), in which excess cardiac mortality was observed in patients treated with tolbutamide or phenformin, compared to patients treated with diet alone. As stated in the labeling, the interpretation of the UGDP results has been the subject of controversy, but led to the Special Warning extending to the biguanide and sulfonylurea classes of drugs.

The recent publications of the results of the United Kingdom Prospective Diabetes Study (UKPDS) now indicate that intensive glycemic control with metformin did not increase the risk of cardiovascular mortality in patients with type 2 diabetes. Therefore, we are now proposing that the Special Warning be deleted from the Glucophage® package insert.

The current submission includes: 1) A discussion paper which puts results of the UGDP and UKPDS into perspective; 2) proposed draft labeling with deletion of the Special Warnings section and the related item in PATIENT INFORMATION; and 3) copies of the UKPDS publications.

If you have any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

WCR/jsb/lp
Desk Copy: Dr. Robert Misbin (HFD-510, PKLN 14B-04)
Ms. Jena Weber (HFD-510, PKLN 14B-04)

REVIEWS COMPLETED
CSO ACTION: [X] LETTER [ ] N.A.L. [ ] MEMO
/S/ 3/22/99
CSO INITIALS DATE

Not /S/ 3/19

Jena -
Pls notify BMS that the lit. reports quality as clinical data for UF and they are required. Therefore, they need to pay for a suppl. w/ CLIN data & get a new UFID & submit a new UF Cover Sheet. Also, you should draft an "UN" letter. Tx, /S/

The revised labels (SLNs UDCP waiving) should be waived.

/S/
3/11/99

Walt /S/ 3/31/99